REMARKS

Status of Claims

Claims 1-15 and 17-20 stand rejected.

Claims 1, 3-15, 17-19 are currently amended.

New claims 66-80 have been added.

Claims 1-15, 17-20 and 66-80 are currently pending.

Objection to the Specification - Priority

In the Office Action dated January 30, 2003, it is said that the earliest priority date of the instant application is that of U.S. Provisional Patent Application No. 60/229,071, August 30, 2000. Applicant respectfully traverses and asserts that the present application is entitled to a priority date at least as early as the filing date of U.S. Provisional Patent Application No. 60/208,348, May 31, 2000. At least original claim 1 and new claim 77 are fully supported in the specification of 60/208,348. See, for example, page 5, last paragraph, of 60/208,348, which states,

> In preparation for this application, we conducted studies to demonstrate that IgA in the plasma of female SD-rats is significantly reduced at the time when carcinogenesis is most effective. ... These data indicate that rat and human females have the same "window" with regard to IgA.

Without waiving the right to claim the benefit of the 06/203,314 filed May 10, 2000, at Applicant's option, in a continuing application, Applicant has amended the paragraph of the specification headed "Cross-Reference to Related Applications" so as to omit reference to provisional application no. 60/203,314.

Rejections Under 35 U.S.C. § 112, Second Paragraph.

In the Office Action, Claims 1-15 and 17-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. With respect to claim 1, the Examiner considers the term "predetermined standard" vague and indefinite. Applicant believes that, with the benefit of Applicant's disclosure, one of skill in the art would have the necessary skills to arrive at or select a standard for comparison (*e.g.*, normal IgA, IgM levels of healthy individuals) in the claimed method, without undue experimentation. For example, the *Garde et al.* reference cited by the Examiner reports on page 555 average levels of plasma IgA under various biological conditions in healthy individuals. Nevertheless, without narrowing the scope of the claim, claim 1 is currently amended to omit the objectionable term. Claims 6 and 17 have been amended similarly.

With respect to claim 5, the terms "predetermined population," "predetermined amount of steroid hormone," "predetermined amount of steroid hormone free specimen," "predetermined period of time," "significant increase" and "significant lack of increase" are vague and indefinite according to the Examiner. Claim 5 has also been amended to omit most of the terms in question. Applicant respectfully traverses the Examiner's suggestion that the terms "significant increase" and "significant lack of increase" are not defined by the claim. Applicant believes that one of skill in the art would be familiar with conducting and evaluating cell proliferation assays and would possess the necessary skills to recognize when a difference between two cell counts is significant. Specific guidance for understanding the meaning of the term "significant" is found in Applicant's specification, at paragraph 222, for instance. Applicant states, with respect to a cell proliferation assay using an estrogen responsive cell line, that "[t]he significance of differences between test dishes and controls was evaluated by the student's *t* test. Values of $p < 0.05$ were accepted as significant." Student's t-test is a usual statistical tool for this purpose. An additional non-narrowing amendment to claim 5 makes it clearer that it is the difference in cell number that is being measured. This amendment merely makes explicit that which was implicit in the original claim. New claim 66, which depends from claim 5, has been added to specifically require a statistical difference of $p < 0.05$ between cell population counts.

With respect to claim 8, the Examiner is of the opinion that without a specific limitation that would define the term "suitable *in vitro* cell culture assay," the metes and bounds of the claim cannot be determined, according to the Examiner. Although Applicant has described suitable assays, including appropriate medium for culturing various cell types (see for example, paragraph 312 in the specification), the term in question can be omitted from the claim without narrowing the scope of the claim. Accordingly, claim 8 now recites that a test may be carried out on the poly-Ig receptor for mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth, and has also been amended to require determining that the poly-Ig receptor is capable of mediating immunoglobulin inhibition of steroid hormone responsive cell growth wherein the inhibition of steroid hormone responsive cell growth is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth. This rewording of the claim language makes the intended meaning clearer.

New claim 67, which depends from claim 8, has been added to specifically recite IgA or IgM as the inhibitors. As discussed in more detail below, with respect to the rejection under 35 U.S.C. § 102(b), the Fcγ portion of claim 8 has been deleted and reintroduced as new claim 68 in order to better focus on certain issues which might remain in controversy.

Claim 12 is considered indefinite because it does not recite a step linking an action of the secretory immune system with the negative regulation of breast tissue proliferation. In response, claim

12 has been amended to recite such a link, *i.e.*, "said detecting comprising testing for loss or reduction of steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth."

Regarding claim 13, the Office Action states that it is unclear if the receptor must actively mediate the steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth as part of the method, or if the receptor need only possess the potential ability of being able to mediate said inhibition of cell growth. It is also said that the term "suitable *in vitro* cell culture assay" needs definition or listing of what constitutes said cell culture assay. Currently amended claim 13 has been amended to omit the objectionable term "suitable *in vitro* cell culture assay," and now recites that the method may include determining whether the poly-Ig receptor is capable of mediating immunoglobulin inhibition of steroid hormone responsive cell growth, wherein the inhibition is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth.

The Examiner also takes the position that claim 18 does not specify an active method step that would follow in the case that the cells were stimulated, and does not specify an active method step that would follow in the case that the cells were not stimulated. Accordingly, claim 18 has been amended to clarify that if it is determined that the cells are stimulated by the steroid hormone to proliferate, then certain action is taken. As currently amended, it is also clearer now that in either case (stimulated or not stimulated), one or more of the remaining conditions are determined as part of the claimed method.

Claim 19 is said to be lacking antecedent basis in the first condition of the claim. In response, Applicant has amended claim 19 to more clearly show antecedent basis. Obtaining a specimen from the patient is now required and thus provides clear antecedent basis for subsequent actions in the claimed method. The term "defined standard values" complained of by the Examiner has been omitted without narrowing the claim.

The Examiner also states that it is unclear what "ERg" encompasses in claim 20, but has assumed for the purpose of the examination that ERg would be read as estrogen-related receptor gamma. Applicant's photocopy of the application as filed shows claim 20 as reciting "ERγ" (with the Greek symbol gamma), so it is unknown to Applicant why an apparent typographical error is present in the Examiner's copy of original claim 20. Nevertheless, Applicant confirms the Examiner's interpretation of the intended term.

It is unclear why independent claims 7, 9, 10, 11, 14, 15 and 17 are rejected under 35 U.S.C. § 112, 2nd paragraph, as no specific complaints were set forth with respect to those claims in the Office Action dated January 30, 2002. If Applicant has misunderstood this ground of rejection, an opportunity to respond and re-amend the claims without prejudice is respectfully requested. All of claims 1-15 and

17-20, as currently amended, are believed to fully comply with the requirements of 35 U.S.C. § 112, 2nd paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph.

Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the invention. It is said that the claims are drawn to a genus of molecules encompassing mutant, truncated and otherwise variant poly-Ig or Fc receptor proteins. The Examiner has also stated that the claims do not limit the "defect" in terms of specific structural or specific functional characteristics, thus it is not possible to determine if a given protein is a member of the claimed genus. In response, Applicant has chosen to first amend claim 10 to omit "or a Fcγ receptor gene," and to reintroduce the omitted subject matter as new claim 80, which is like currently amended claim 10 except it omits "a poly-Ig receptor." Claim 10 has been reworded to make it clearer what is meant by "defect." Claims 10 and 80 include limitations for identifying a loss of heterozygosity or an allelic imbalance in a poly-Ig receptor gene, or carrying out site directed mutagenesis in a non-cancer tissue culture cell model whereby a domain of a poly-Ig receptor gene is altered, and then identifying at least one said altered domain that causes loss of ability to mediate inhibition by the immunoglobulin inhibitor. Currently amended claim 10 and new claim 80 also include matching the screened poly-Ig receptor gene (or Fcγ receptor gene) from the cancerous cell to the receptor gene from the non-cancerous cell culture model that contains an altered domain correlated to loss of inhibition mediating ability, such that a genetically defective poly-Ig receptor gene is identified.

Claim 11 has been amended similarly to separate the poly-Ig receptor and Fcγ receptor, and new claim 69 now contains the subject matter pertaining to the Fcγ protein deleted from original claim 11. Both claims 11 and 69 recite that the "defective" receptor protein is coded for by the defective gene identified in claim 10 or 80, respectively. These amendments are supported in the specification, for instance, in Example 38 at paragraphs 536-538.

In the Office Action, claims 1-7, 12, 17 and 18 were also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not sufficiently described in the specification. With respect to claim 7, it is suggested that when given the broadest reasonable interpretation, it encompasses any IgA, IgM or IgG1, including non-secretory antibodies. Claim 7 is currently amended to recite that the immunoglobulin binding that is being assayed is other than antigen-antibody recognition based association. As discussed in paragraph 37 of Applicant's specification, "the cell

growth inhibitory activity of the immunoglobulin inhibitors is a function that is distinct from any additional antibody-antigen recognition type immune activities." Also, see paragraph 400 of the specification, which states,

> "[t]his study yielded the same estrogenic effects with both sources of IgM. Again, the antigenic determinant appears to be unimportant. The results support the view that the heavy chains dictate the activity."

In paragraph 403 of the specification it is stated,

> "[t]wo different types of human IgM were also compared with LNCaP cells (**Fig. 105**). They were plasma derived and myeloma derived IgM. Despite the differences in antigen binding domains, both forms were equally inhibitory and both forms were reversed by 10 nM DHT. These results indicate that the Fc/heavy chain of IgM is the functional activator of the inhibition." [underlining added for emphasis]

New claim 71 is similar to claim 7 except it relates to the Fcγ receptor and to binding of IgG1 or IgG2 by other than antibody-antigen recognition based association.

With respect to claim 12, the Examiner states that secretory endogenous antibodies to exogenous or endogenous tumor antigens which were generated by the immune system, including those antibodies which would react with a cell surface breast tumor antigen, are encompassed by the claim. The Examiner suggests that the specification does not teach how to use the methods dependent on the multitude of antibodies encompassed by these claims. Claim 12 has been amended to clarify that the method requires testing for loss or reduction of immunoglobulin inhibition of steroid hormone responsive cell growth in that tissue, wherein the inhibition is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth. This clarifying amendment now states explicitly what is implicit in the term "steroid hormone reversible immunoglobulin inhibition," and is fully supported by the specification (for example, paragraph 363).

As to claims 1-6, 17 and 18, it is said in the Office Action that Applicant's method is dependent on the identity of a steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth. The Examiner suggests that the art teaches numerous serum factors that cause inhibition of steroid dependent cell growth, and mentions publications by Ghosh et al. (*Indian Journal of Experimental Biology*, Apr. 2000, Vol. 38, pp. 313-322), Das et al. (*Endocrinologia Japonica*, 1976, Vol. 23, pp. 275-279), Sonnenschein et al. (*J Steroid Biochemistry*, 1996, Vol. 59, pp. 147-154, and Tanji et al. (*Anticancer Research*, Jul-Aug 2000, Vol. 20, pp. 2785-2790), as examples. The Examiner also refers to publications that describe variation of IgA levels in healthy subjects, including Garde et al. (*Clinical Chemistry*, 2000, Vol. 46, pp. 551-559) and Gomez et al. (*Amer J Reproduc Immunol*, 1993, Vol. 29, pp. 219-223).

While Applicant agrees that the literature is replete with examples of various "serum factors" that cause inhibition of steroid dependent cell growth, it should be noted that inhibition of steroid hormone dependent cell growth is not the same thing as inhibition of steroid hormone dependent cell growth in which the inhibition can be reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth. As discussed in Applicant's specification (at paragraphs 287 and 456, for example), the immunoglobulin inhibitor in effect blocks all mitogenic action in a steroid hormone responsive cell **except that exerted by the steroid hormones**, and this growth blocking effect can be reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth (paragraph 363).

Applicant respectfully traverses this rejection for at least the reason that **no protein constituent of serum previously described by others that inhibits mucosal cell growth possesses the same "master switch" property as Applicant's immunoglobulin inhibitors and none are steroid hormone reversible in the same way as Applicant's (*i.e.*, its inhibitory activity is reversible by the growth promoting effect of sufficient steroid hormone via its native cellular receptor).** The present inhibitors have been distinguished over the estrocolyones hypothesized by Sonnenschein *et al.* (see paragraph 289 of Applicant's specification, for example).

Tanji *et al.*

As discussed in the specification at paragraph 246, the inhibitory protein described by Tanji *et al.* also behaves quite differently than that of Applicant's claimed methods. The cell growth inhibitor of Tanji *et al.* is not an inhibitor at all until estrogen binds to it. In other words, that inhibitor requires binding of estrogen and albumen to the inhibitor protein in order for the protein to have inhibitory effects. This is a quite different mode of action than steroid hormone reversibility of inhibition. See the Abstract of the Tanji *et al.* publication, for example, where it states,

> While estrogen by itself has no effect on [MCF-7 cell] growth, estrogen in the presence of added serum inhibits cell growth through a mechanism not mediated via nuclear estrogen receptors.

That statement in itself is puzzling since MCF-7 cells are well known in the art to be estrogen responsive for cell growth (*see* paragraph 507 of Applicant's specification and the Lemieux and Fuqua reference cited therein). Clearly the mechanism for inhibiting cell growth described by Tanji *et al.* is very different than that of Applicant's inhibitors.

Contrast the teachings of Tanji *et al.* with paragraph 361 of Applicant's specification, for example.

> The fact that proteins in CA-PS-pool II [the partially purified immunoglobulin inhibitor fraction] bind steroids is not germane to the mechanism of action of these hormones in growth regulation under physiological conditions.

The Tanji *et al.* reference also mentions an estrogen independent protein that is related to the estrogen dependent inhibitor. Both of those proteins are said to cross-react with antibodies to SHBG (p. 2788, col. 2, par. 3 of Tanji *et al.*), whereas Applicant has clearly established that the immunoglobulin inhibitors of the claimed methods are not SHBG (see the discussion in paragraphs 345 and 360 - 361 of the specification, for example). As proof positive, horse and rat, which are known to be devoid of SHBG, were purposely selected as sources for isolating Applicant's inhibitors (as discussed in the specification at paragraph 343).

The terms "immunoglobulin inhibitor" and "steroid hormone reversible immunoglobulin inhibitor" are described and defined in paragraphs 18, 363 and elsewhere throughout the specification. The distinction is made even clearer in the currently amended claims which recite wherein the inhibition is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth. It is plain that the proteins described in the cited references are not the same as the immunoglobulin inhibitor of claims 1-6, 17 and 18.

Applicant submits that claims 1-7, 10-12, 17 and 18 are all in compliance with 35 U.S.C. § 112, first paragraph.

Normal IgA Levels.

The Examiner further states that it is known that levels of IgA can vary in an individual over time, and that there can be large variations between healthy subjects (citing Garde et al. *Clinical Chemistry*, 2000, Vol. 46, pp. 551-559). Referring to Gomez et al. (*Amer J Reprod Immunol*, 1993, vol. 29, pp. 219-223), the Examiner also states that levels of secretory IgA are hormonally regulated and thus variable over the course of the menstrual cycle. Taking the position that the specification lacks teachings regarding ranges or levels of secretory immunoglobulins that were indicative of normal individual(s) having a steroid hormone responsive disease, the Examiner suggests that one of skill in the art would not know how to use the claimed methods without undue experimentation.

In response, Applicant respectfully traverses this rejection. The Examiner has pointed out that levels of IgA in healthy individuals have been well documented in the literature. Given the teachings of Applicant's specification, one of ordinary skill in the art could readily recognize when an IgA test result is lower than established "normal" values, even taking into account the documented seasonal, daily and biological variations in healthy individuals. The artisan would also know when an IgA test result was in a relatively low range or high range of the documented ranges for healthy individuals. For

example, it is well known that an individual's immune system can be compromised in a variety of ways and for a number of reasons. No undue experimentation is needed for the artisan to be able to practice the claimed methods. Moreover, in light of Applicant's disclosure, detecting a substantial or total lack of immunoglobulin inhibitors (*e.g.*, IgA and IgM) would be highly suggestive of increased risk for developing breast cancer (claim 1). Although Applicant believes that the meaning of "predetermined standard" is sufficiently clear to one of skill in the art endeavoring to practice the claimed invention, the claims have nevertheless been amended and reworded so as to avoid use of "predetermined" without narrowing the scope of the claims.

Rejections Under 35 U.S.C. § 102(b).

Claims 8 and 68.

In the Office Action claim 8 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Krishnan *et al.* (*Prevention and Detection of Cancer*, 1977, Nieburgs, Ed., pp. 449-453). According to the Examiner, Krishnan *et al.* disclose a method for detecting Fc receptor activity in various breast carcinoma tissues by an agglutination assay with sheep erythrocytes sensitized with IgG. The Examiner further states:

> [i]t is inherent in the method of Krishnan et al. that the Fc receptor on the breast carcinoma cells is the mediator of steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth as that is what is taught by the instant specification. The Fc receptor in breast carcinoma tissue would be capable of mediating steroid hormone reversible inhibition in a suitable cell culture assay.

In order to more clearly focus the issues, Applicant has amended claim 8 to omit "or an Fcγ receptor," and the omitted subject matter of claim 8 is now presented in new claim 68, which is like claim 8 except it omits "a poly-Ig receptor." Claim 8, as currently amended, clearly distinguishes over the Krishnan *et al.* reference at least for the reason that the reference does not teach a method that employs a poly-Ig receptor.

Applicant's new claim 68 requires determining that the Fcγ receptor is a functional mediator of immunoglobulin inhibition of steroid hormone responsive cell growth wherein the inhibition is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth. Claim 68 also includes the option of testing the Fcγ receptor for inhibition mediating activity. The MPEP 2131 states,

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

All of the claim limitations are not expressly or inherently described in Krishnan *et al.* Even if a native Fcγ receptor in breast carcinoma tissue would be inherently capable of mediating steroid hormone reversible inhibition in a suitable cell culture assay, that would not anticipate a new process of using that Fcγ receptor where the "normal" use of the Fcγ receptor does not perform the claimed method. See MPEP 2112.02. For instance, a regular assay for simply detecting an Fcγ receptor would not inherently also include detecting whether that particular -- or any – Fcγ receptor was capable of mediating inhibition of cell growth by an immunoglobulin. There is absolutely no teaching in Krishnan *et al.* of testing for inhibition mediating activity, or of determining that any such inhibition was capable of being reversed by associating a steroid hormone with a cellular steroid hormone receptor that is active for promoting cell growth. Thus, the artisan could not achieve the method of claim 68 by carrying out the method of Krishnan *et al.*

With respect to claim 8, in the Office Action it is stated that Hein *et al.* (PCT Publication WO 99/20310) discloses the detection of a poly-Ig receptor on an epithelial cell by means of a targeting molecule. The Examiner suggests that the poly-Ig receptor would inherently have the capability of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable *in vitro* culture assay. Applicant has amended claim 8 to require determining that the poly-Ig receptor is a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth. Amended claim 8 also includes the option of testing the poly-Ig receptor for inhibition mediating activity.

Without prior knowledge of Applicant's disclosure, one of ordinary skill in the art would not know or even suspect that a poly-Ig receptor could function as described in the claims. All of the claim limitations are not expressly or inherently described in Hein et al. Even if a native poly-Ig receptor would be inherently capable of mediating steroid hormone reversible inhibition in a suitable cell culture assay, that would not anticipate a new process of using that receptor where its normal use does not include the claimed method. See MPEP 2112.02. For example, Hein et al. do not teach a method that includes determining that a poly-Ig receptor is a mediator of steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth. There is no teaching in Hein et al. of testing a poly-Ig receptor for *in vitro* activity for mediating steroid hormone reversible inhibition of steroid hormone responsive cell growth. As a result, one could not achieve the method of claim 8 by simply carrying out the method of Hein et al.

Claims 9 and 72.

Claim 9 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Kimberly *et al.* (WO97/46715). In the Office action it is stated that Kimberly *et al.* disclose a method for detecting the

Fcγ receptor in a mucosal epithelial cell comprising detection of the Fcγ gene. The Examiner suggests that the Fcγ receptor of an epithelial cell would inherently have the property of being a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth. As with claim 8, Applicant has chosen to separate the portion of original claim 9 that relates to the poly-Ig receptor gene from the portion that relates to the Fcγ receptor gene. Accordingly, new claim 72 now contains the subject matter of claim 9 except for that portion that relates to the poly-Ig receptor gene. Both of these claims require not only detecting the presence of a poly-Ig receptor gene (or Fcγ gene) in a mucosal epithelial cell, but also requires determining whether a poly-Ig receptor (or Fcγ receptor) encoded by said gene has the property of being capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth. Without prior knowledge of Applicant's disclosure, one of ordinary skill in the art would not know or even suspect that a poly-Ig receptor or an Fcγ receptor could function as described in the respective claims. There is no step in Kimberly *et al.* of determining whether a poly-Ig receptor (or Fcγ receptor) encoded by the gene has the property of being capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth. As a result, one could not possibly achieve the method of claim 9 or new claim 72 by following the disclosure of Kimberly *et al.* For at least these reasons, currently amended claim 9 and new claim 72 distinguish over the cited reference.

Claim 19.

Claim 19 is also rejected under 35 U.S.C. § 102(b). In the Office Action it is stated that either Becchis *et al.* (Breast Cancer Research and Treatment, 1999, Vol. 54, pp. 101-107) or Markowitz *et al.* (U.S. Patent No. 5,866,323) anticipate the claim. The Examiner suggests that by disclosing a method of detecting the SHBG variant in plasma that correlates with the presence of ER^+/PR^+ tumors, Becchis *et al.* fulfill the specific embodiments of claim 19 with regard to the lack of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth (the lacking inhibitor being wild-type SHBP). Applicant respectfully traverses this rejection for the reason that an "immunoglobulin inhibitor" as defined by Applicant in the specification (paragraphs 18, 343 - 347 and 363, for instance) is plainly not the same as the SHBP of Becchis *et al.* Claim 19 has been amended to explicitly state that which was previously implicit in the claim, *i.e.*, that the immunoglobulin inhibitor is an "immunoglobulin inhibitor of steroid hormone responsive cell growth wherein inhibition by said immunoglobulin inhibitor is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth." It is explained in Applicant's specification that SHBG does not possess the property of inhibiting growth (proliferation) of a steroid responsive cell, much less doing so in manner that is reversibl by a steroid hormone as recited in

claim 19. See, for example, the above discussion of SHBG with respect to the rejections under 35 U.S.C. §112, the data reported in paragraph 359 of the specification, and amended paragraph 343 of the specification, where Applicant states:

> However, in view of the results presented herein and in U.S. Patent App. No. 09/852,958/PCT/US2001/15183, SHBG was considered an unlikely candidate for the inhibitor. Both CDE-horse serum and CDE-rat serum contain concentrations of inhibitor about equal to any of the other serum types investigated but they do not contain SHBG.

Thus, a method detecting the absence of the wild-type SHBP described by Becchis *et al.* cannot anticipate the method of claim 19.

The Examiner goes on to suggest that Becchis *et al.* also fulfills the specific embodiment of aiding in the prognosis of a mammalian cancer patient as correlation with ER^+ and/or PR^- status is indicative of a better prognosis. Applicant agrees that it is generally accepted that ER^+ and/or PR^- status tends to correlate with better prognosis in a breast cancer patient. Nevertheless, the detection of a variant SHBG, the presence of which correlates with ER^+ and/or PR^- status, as taught by Becchis *et al.*, is not the same thing as determining the lack of a cell growth inhibitory amount of "at least one immunoglobulin inhibitor of steroid hormone responsive cell growth wherein inhibition by the immunoglobulin inhibitor is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth in a specimen," as explained above.

Claim 19 has been amended to require "determining the lack of a cell growth inhibitory amount of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth wherein inhibition by the immunoglobulin inhibitor is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth" in a specimen; and, additionally, one or more of the other conditions listed in the claim. One of those additional conditions is determining loss or diminution of a TGFβ receptor in the neoplastic cells. Markowitz et al. do not disclose a method that requires determining the lack of a cell growth inhibitory amount of at least one steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth in a specimen of neoplastic cells in addition to determining the quantity of a functional TGFβ receptor. It can be concluded that the method of Markowitz et al. is different than that of currently amended claim 19.

For at least the foregoing reasons, claims 8, 9 and 19 distinguish over the cited references.

Conclusion

Applicant may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other distinctions between the claims and the prior art, which have yet to be raised, but which may be raised in the future.

Applicant believes that all claims are free of the prior art and are in condition for allowance. Entry of the amendments and allowance of all pending claims is respectfully requested. In the event that an extension of time is necessary in order for this submission to be considered timely filed, please consider this a Request for Extension of Time, and the Commissioner is authorized to charge the fee under 37 C.F.R. § 1.17(a) to Deposit Account 03-2769 of Conley Rose, P.C., Houston, Texas. If the Examiner believes that a telephonic interview would be beneficial, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted:

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